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Unexpected outcome (positive or negative) including adverse drug reactions

Acute liver impairment after sodium valproate overdose

[William Stephen Waring](#) and [Andrew C Nixon](#)

The Royal Infirmary of Edinburgh, Scottish Poisons Information Bureau, 51 Little France Crescent, Edinburgh EH16 4SA, UK

William Stephen Waring, Email: s.waring@ed.ac.uk

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Abstract

Liver impairment is a recognised adverse effect of long-term sodium valproate treatment, but there are few reports concerning its occurrence after acute overdose. This report describes a 36-year-old woman who deliberately ingested 32 g of sodium valproate (Epilim). Serum valproate concentration was 4370 $\mu\text{mol/l}$ (630 mg/l) at 4.3 h post-ingestion (therapeutic reference range: 300–600 $\mu\text{mol/l}$), and the elimination half-life was 14.1 h. Liver biochemistry tests were initially normal but gradually became impaired, and highest alanine aminotransferase (761 U/l) occurred 2.3 days after ingestion. Supportive measures alone were sufficient to allow recovery of liver function. This case indicates that sodium valproate overdose may cause acute hepatocellular injury, even in the absence of pre-existing liver disease.

Background

Sodium valproate is a branch-chained fatty acid (2-n-propylpentanoate) that is used to treat a variety of seizure types including generalised seizures, atypical absences and myoclonic jerks. Its mechanisms of action are not fully understood, but valproate evokes pharmacological effects that include enhanced γ -aminobutyric acid (GABA) synthesis and release, diminished activity of the excitatory amino acids γ -hydroxybutyrate and glutamate, and blockade of voltage-dependent sodium channels.¹ The usual dosage is 1–2 g daily in divided doses, and peak serum concentrations occur 2–3 h after standard oral formulations and 5–10 h after sustained-release preparations. Valproate is subject to extensive hepatic metabolism, and the plasma elimination half-life is around 9–18 h.

Adverse effects of valproate include nausea, tremor, ataxia, hair loss, weight gain and hyperammoniaemia in 20–50% of cases. Elevated liver enzymes occur in more than one third of patients.² Liver failure is a recognised adverse effect, and risk factors include age <2 years, inherited metabolic disorders (eg, mitochondrial disease) and pre-existing liver disease.³ Liver enzymes are normally assessed before and at least 6 months after initiating treatment, and valproate is contraindicated in patients with active liver disease.

After valproate overdose, recognised features of toxicity include ataxia, tremor, central nervous system depression, gastrointestinal disturbance, acute pancreatitis, metabolic acidosis and hyperammoniaemia.

In severe cases, seizures, respiratory depression, coma and severe acid-base and electrolyte disturbances may occur.^{3,4} In contrast to therapeutic administration, hepatotoxicity is rarely reported after acute valproate overdose.⁵

Case presentation

A 36-year-old woman presented to the emergency department 2 h after a stated ingestion of 32 g of sodium valproate (Epilim, Sanofi-Aventis). She denied any co-ingested drugs or ethanol, and was accompanied by empty drug packaging that corresponded with the stated quantity ingested. Past history included learning difficulties in childhood, depression 4 years before, and suspected generalised seizures for which sodium valproate 500 mg twice daily had been prescribed; she had been seizure-free in the preceding year.

Conscious level was normal (Glasgow Coma Scale 15), and tone, power and reflexes were normal and symmetrical. Temperature was 36.3°C, heart rate 72 min⁻¹, respiratory rate 16 min⁻¹, blood pressure 128/72 mm Hg, peripheral oxygen saturation 97%, and a 12-lead electrocardiogram was normal. Breath alcometer did not detect ethanol, and investigations showed alanine transaminase 27 U/l, alkaline phosphatase 56 U/l, γ -glutamyltransferase 9 U/l, bilirubin 5 mmol/l, urea 6.2 mmol/l and creatinine 68.6 μ mol/l. Serum electrolytes, full blood count and coagulation were normal. Neither paracetamol nor salicylates were detected in blood, and a urine sample was negative for amphetamines, benzodiazepines, cannabinoids, cocaine metabolites, methadone and opiates.

The patient was admitted to the toxicology unit for further clinical monitoring and psychiatric evaluation. At around 36 h after ingestion, the patient complained of nausea and vague abdominal pain. Repeat clinical examination was normal, but laboratory investigations showed increased serum alanine transaminase activity and bilirubin concentration. These continued to rise, and the highest recorded alanine transaminase activity was 761 U/l with a corresponding bilirubin concentration 26 mmol/l at 2.3 days after ingestion ([fig 1](#)). Alkaline phosphatase, γ -glutamyltransferase, serum electrolytes and bicarbonate, coagulation, renal function and haemodynamic variables remained normal.

Outcome and follow-up

Symptoms had settled by day 4, and the patient was discharged home on day 7 when liver enzyme levels were falling. Valproate concentrations were later confirmed as being very high ([fig 2](#)). Six weeks later, the patient was asymptomatic and liver biochemical tests were normal (alanine transaminase 16 U/l, alkaline phosphatase 54 U/l, γ -glutamyltransferase 12 U/l, bilirubin 14 mmol/l).

Discussion

Abnormal liver biochemistry was attributed to sodium valproate overdose because of the strong temporal relationship, valproate concentrations in a toxic range, and the lack of co-ingested drugs or ethanol. Maximal derangement of liver enzymes was noted at 2–3 days after ingestion, by which time valproate concentrations had fallen to a non-toxic level. Acute liver impairment has been reported in only a small number of cases of sodium valproate overdose and not as an isolated finding. A unique feature in the present case is that initial liver biochemistry tests were normal. Therefore, acute liver impairment was caused by sodium valproate overdose rather than as a result of previous therapeutic administration. The time course of the hepatic enzyme rise was similar to that of other types of drug toxicity, for example paracetamol.⁶ Coagulation was normal, indicating that hepatic function was normal despite acute liver injury as indicated by hepatic enzyme elevation.

Sodium valproate is predominantly metabolised by hepatic P450 cytochromes and glucuronidation,

while a minor component involves mitochondrial oxidation similar to other long-chain fatty acids. After administration of higher valproate doses, mitochondrial omega oxidation is more extensive, and the carnitine shuttle plays a greater role. This involves a number of metabolic steps, including translocation of valproylcarnitine into the mitochondrial matrix and formation of valproyl-coenzyme A within the mitochondria.⁷ The latter is thought to play a major role in the development of hepatotoxicity, although other metabolic intermediates including 2-en-valproate, 4-en-valproate and 2,4-dien-valproate have also been implicated.⁸ Carnitine is involved in the regulation of long-chain fatty acid metabolism by regulating the availability of free coenzyme A within the mitochondrion. Valproate may cause carnitine deficiency by inhibiting biosynthetic enzymes and impairment of intracellular carnitine transport.⁹ Carnitine deficiency may be an important mechanism related to valproate toxicity.

Clinical management of valproate overdose generally consists of supportive care, ensuring adequate hydration, and correction of electrolyte or acid-base disturbance. Activated charcoal should be considered if patients present to hospital within 1 h of ingestion, and gastric lavage should be considered only if patients present within 1 h of ingesting a life-threatening quantity (for example >400 mg/kg). While there are theoretical reasons why activated charcoal beyond 1 h might be helpful, there are no clinical data to support this. Charcoal was not administered to this patient because the interval between ingestion and presentation was >1 h. Patients should normally be observed for at least 12 h after ingestion, and longer if symptoms develop. Patients should have electrolytes and liver biochemistry checked and, in severe poisoning, ammonia and acid-base status need to be monitored. Intravenous carnitine administration has been reported to alleviate features of toxicity in some patients, and should be considered in patients with encephalopathy, severe hyperammoniaemia, and liver impairment.^{10,11} Extracorporeal techniques, for example the molecular adsorbent recirculating system (MARS), have been used to support poisoned patients with liver toxicity, but these have not been studied in the setting of valproate toxicity.¹²

The elimination half-life given by the slope of the best-fit exponential decay curve was 14.1 h, which is similar to another recent report of sodium valproate overdose (11.5 h) and consistent with values reported after therapeutic doses.¹³

Learning points

- Hepatotoxicity may occur as an acute toxic effect after sodium valproate overdose, even in the absence of pre-existing liver impairment.
- Clinical features and laboratory abnormalities might not be apparent at the time of presentation to hospital, and patients should be observed for at least 12 h after ingestion.
- Elimination half-life after overdose is similar to therapeutic doses, suggesting linear kinetics in the toxic dose range.

Footnotes

Competing interests: none.

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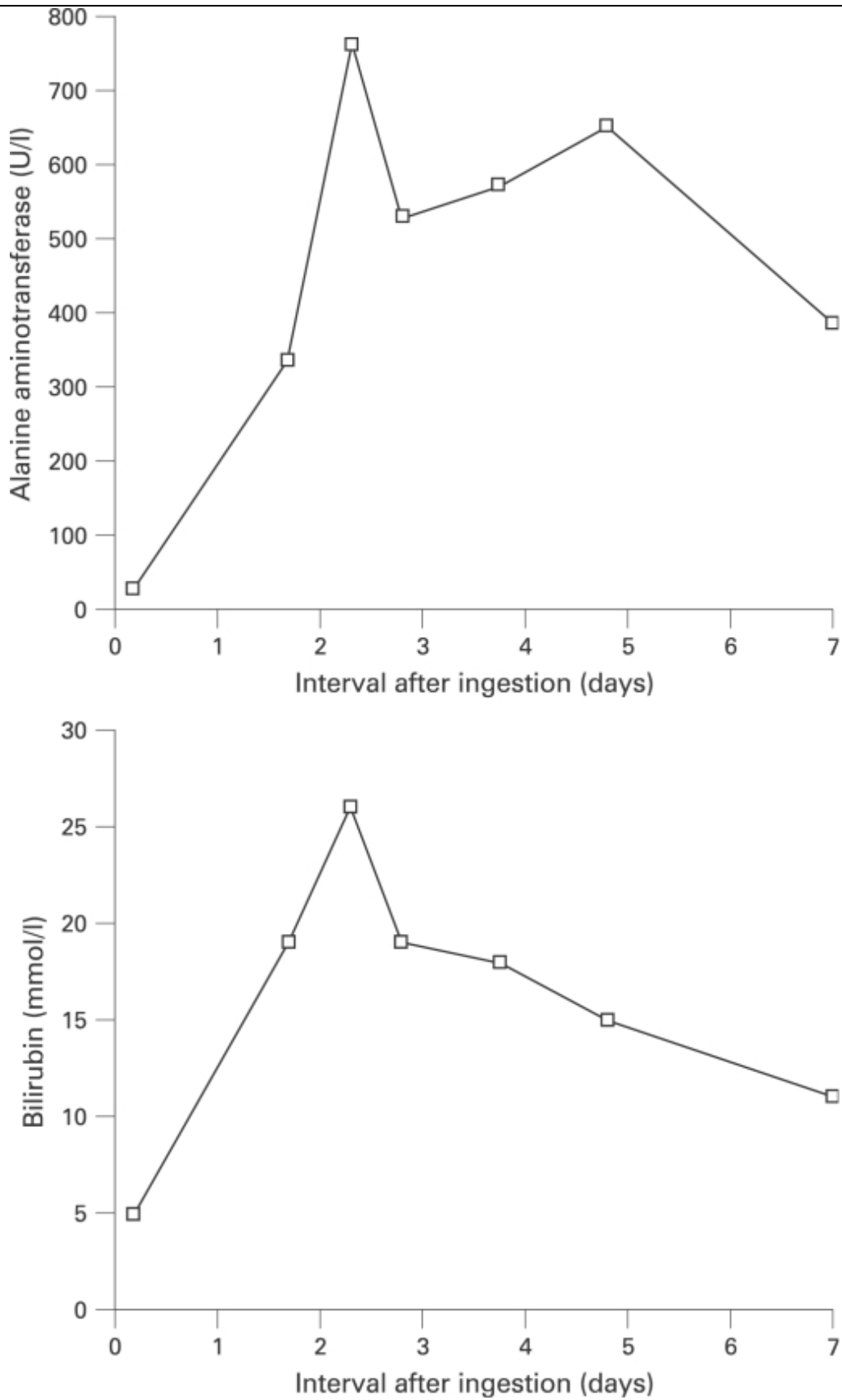
Figures and Tables

Figure 1

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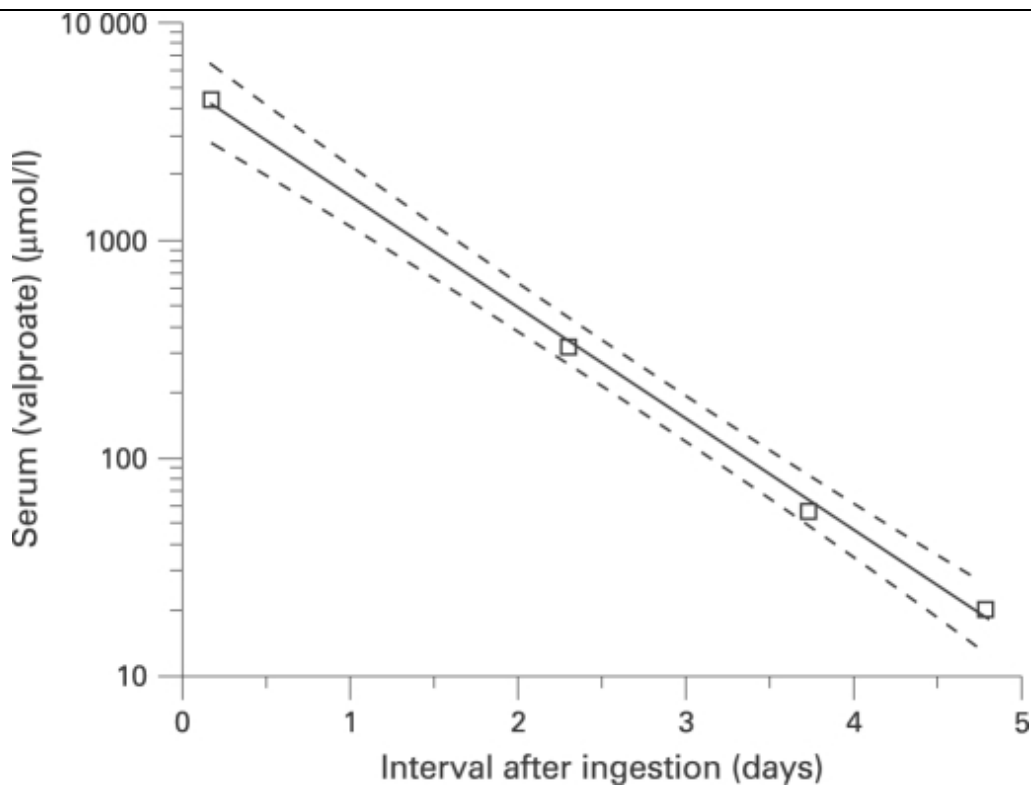
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Serum alanine transaminase activity and bilirubin concentration determined at various intervals after sodium valproate overdose.

Figure 2



Serum valproate concentrations determined at various intervals after overdose, shown with exponential best-fit line ($y=5145\times e^{-1.1784x}$) and broken lines indicating 95% confidence intervals around the best fit line; the normal therapeutic range for valproate is 300–600 µmol/l (50–100 mg/l).

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